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Mechanisms by which calcium receptor stimulation modifies electromechanical coupling in isolated ventricular cardiomyocytes

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Abstract

The calcium-sensing receptor (CaR) is widely expressed throughout the entire cardiovascular system and is capable of activating signaling pathways in different cells. Alongside calcium, the CaR also responds to physiological polycations such as putrescine underlining a participation in physiological and pathophysiological processes. Here, we aimed to determine mechanisms as to how CaR activation affects the contractile responsiveness of ventricular cardiomyocytes under basal and stimulated conditions. For that purpose, cardiac myocytes from 3-month-old male Wistar rats were isolated, and the acute effects of an antagonist (NPS2390), agonists (putrescine and gadolinium), or of downregulation of the CaR by siRNA on cell shortening were recorded in a cell-edge-detection system. In addition, experiments were performed on muscle stripes and Langendorff preparations. Mechanistic insights were taken from calcium transients of beating fura-2 AM-loaded cardiomyocytes and western blots. Isolated ventricular cardiomyocytes constitutively express CaR. The expression in the atria is less pronounced. Acute inhibition of CaR reduced basal cell shortening of ventricular myocytes at nearly physiological levels of extracellular calcium. Inhibition of CaR strongly reduced contractility of ventricular muscle stripes but not of atria. Activation of CaR by putrescine and gadolinium influences the contractile responsiveness of isolated cardiomyocytes. Increased calcium mobilization from the sarcoplasmic reticulum via an IP3-dependent mechanism was responsible for amplified systolic calcium transients and a subsequent improvement in cell shortening. Alongside with these effects, activation of CaR increased relaxation velocity of the cells. In conclusion, ventricular CaR expression affects contractile parameters of ventricular heart muscle cells and modifies electromechanical coupling of cardiomyocytes.

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Keywords

Calcium transients, Calcium-sensing receptor, Cardiomyocytes, Contraction, Gadolinium, IP3 receptor, Polyamines, Protein kinase C, Sarcoplasmic reticulum